A Phase II Randomized Study of GM-CSF Gene-Modified Autologous Tumor Vaccine (CG8123) with and without Low-Dose Cyclophosphamide in Advanced Stage Non-Small Cell Lung Cancer

Non-technical Abstract

There are about 170,000 new cases of lung cancer in the United States each year and almost 160,000 annual deaths. Lung cancer remains the leading cause of cancer-related death in both men and women in North America. Although early stage disease is curable in some patients by surgery, more than two-thirds of patients have advanced stage disease at diagnosis that is fatal in > 90% of patients despite existing therapies. Approximately 75% of lung cancer cases are made up of non-small cell lung cancer (NSCLC) subtypes. By far the greatest risk factor for development of lung cancer is tobacco use.

The currently accepted treatment for patients with advanced stage NSCLC is combination chemotherapy that has been shown to prolong survival minimally, improve quality of life, and decrease health care costs, compared with supportive care alone. However, the absolute benefits of chemotherapy for NSCLC are small (overall improvement in survival of -2-3 months) and chemotherapy is associated with significant side effects. Clearly, there is still a need for new therapies that work better and have fewer side effects than chemotherapy.

Two clinical trials have been conducted in NSCLC using a cancer vaccine composed of tumor cells genetically modified to secrete GM-CSF (CG7773). A cancer vaccine is a product that stimulates the immune system so that it recognizes cancer cells as foreign and kills them. GM-CSF is a substance made by the body that helps the immune system recognize a tumor cell and destroy it. In both trials tumor vaccines were generated from the patient's own tumor, and the GM-CSF gene was delivered to the cells using a weakened adenovirus vector. Adenovirus vectors are derived from a common cold virus and can enter cells and deliver new genes. The vaccine cells were irradiated to prevent them from growing or dividing following injection back into the patient. The cells themselves are **not** radioactive. The cells were stored frozen until the day of vaccination. The results of the two clinical trials are described below:

In the first trial, 1 of 33 treated patients had a mixed tumor response. Two additional patients in whom all known tumor sites were removed for vaccine generation have remained without evidence of new tumor growth for over three years. In the second trial, 3 of 33 patients with advanced stage disease who received vaccine treatment achieved long-lasting, complete tumor responses and 3 additional patients had mixed or minor tumor responses. In both trials, the vaccine was well tolerated with the most common side effect being mild redness, itching, and swelling at the vaccine site in >90% of patients. Less common side effects possibly related to the vaccine included mild flu-like symptoms, stuffy nose, and weight loss. Serious side effects reported as possibly related to vaccine treatment included pneumonia, fluid around the heart, dehydration, and fever.

Based on these encouraging results, we have now initiated an additional study of a slightly modified version of this vaccine platform (CG8123) in NSCLC. Several changes to the manufacturing process have been made compared to the CG7773 vaccine used in the previous trials including a slightly modified adenoviral vector containing the GM-CSF gene, removal of animal proteins from the process, and use of a more efficient closed system for all steps of the process. The primary objective of this study is to measure the anti-tumor activity of low doses of cyclophosphamide (a chemotherapy drug) given with the vaccine compared to vaccine alone. It has previously been reported that low doses of cyclophosphamide can increase vaccine-induced anti-tumor immune responses by blocking the activity of cells that suppress these immune responses.

In the current clinical trial patients undergo a surgical procedure to harvest tumor for vaccine production. CG8123 vaccine is manufactured at a central facility. Approximately 4 weeks after the tumor harvest procedure the vaccine is ready for patient use. Patients are then randomized to receive either cyclophosphamide with vaccine or vaccine alone. All patients will receive five vaccines given two weeks apart. Patients that are randomized to the chemotherapy arm will receive cyclophosphamide one day prior to the first, third and fifth vaccination. All patients will then be followed for up to two years.

The success of the study will be measured by looking at several endpoints, including overall vaccine manufacturing success, the safety of vaccine administration alone and with cyclophosphamide, vaccine activity, and quality of life. Measurements of vaccine activity will include immunologic response (skin reactions to injections of the patient's own tumor cells and the presence of anti-tumor antibodies), tumor shrinkage, and time to disease progression and death.

This study is currently open for enrollment.